REMARKS

Claims 1-20 are pending in the application and have been examined. The allowance of Claims 14-20 and the allowability of Claims 10-13 if rewritten in independent form including all the limitations of the base claim and intervening claims is noted with appreciation. Claims 1-9 stand rejected. The specification and Claim 1 have been amended, and new Claim 21 has been added. No new matter has been added. Applicant respectfully requests reconsideration and allowance of Claims 1-9 and 21.

The Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1-9 under 35 U.S.C. § 112, second paragraph, as being indefinite because of the presence of the phrase "such as" in Claim 1. Claim 1 has been amended to delete the phrase "such as NADH, NADPH, or ATP." Withdrawal of this ground of rejection is respectfully requested.

The Rejection of Claims Under 35 U.S.C. § 102

The Examiner has rejected Claims 1-9 under 35 U.S.C. § 102(a) and (b) as being anticipated by Corey et al. (1997) *J. Immuno. Methods* 207(1):43-51. According to the Examiner, Corey et al. discloses the assay of Claim 1. Applicant respectfully disagrees.

Claim 1, from which Claims 2-9 depend, is directed to a method of measuring cell death or membrane damage comprising the step of "determining in a sample of a mixture of dead and living cells or a supernate from the mixture the concentration of a high-energy molecule by a luminescent reaction employing a luciferase, wherein an enzyme or enzymes is naturally present in the living cells being studied, and when released from the dead cells, increases or decreases the concentration of the high-energy molecule by a reaction or reactions, whereby all the reactions necessary to produce the light output are initiated when the sample is contacted with a

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single reagent mixture." Corey et al. does not disclose or suggest all the limitations of Claim 1, as described below.

First, Corey et al. does not describe an assay that may be used both in a sample of a mixture of dead and living cells and in a supernate from the mixture, as recited in Claim 1. Rather, the method disclosed in Corey et al. requires a physical separation of the live cells from the test mixture prior to performing the assay (see Corey et al., page 47, Column 1, stating that the mixture was "centrifuged at 1000 g for 5 min. 5 μL of the supernatant were removed and added to the GP cocktail"). As described in the specification, the separation of the cells from the supernatent is a serious drawback to the prior art methods such as that disclosed in Corey et al. (specification, page 7, lines 14-17; page 8, lines 8-11; page 14, lines 16-18; page 15, lines 2-6). In contrast to the method disclosed in Corey et al., the method of Claim 1 does not require physical separation of the cells, because the reagents have been altered to make the reaction cocktail compatible with the presence of live cells specification (specification, page 15, lines 1-9). For example, it was found that inclusion of the cell culture medium IMDM produced a reaction cocktail that was compatible with the presence of live cells and had excellent sensitivity (see, e.g., EXAMPLE 1, page 32, lines 10-25). For this reason, Corey et al. neither discloses nor suggests all the limitations of Claim 1.

Second, Corey et al. does not disclose or suggest that "all the reactions necessary to produce the light output are initiated when the sample is contacted with a single reagent mixture," as recited in Claim 1. The method disclosed in Corey et al. involves a minimum of two mixing steps, with three steps recommended as a practical minimum (Corey et al., page 45, Column 2; specification, page 14, lines 11-20). These steps are in addition to the cell-separation step described above. In the present invention, all these processes are replaced by a single mixing step, in which all components of the optimized cocktail are added and no separations or

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further transfers are required prior to readout (specification, page 13, line 19 to page 14, line 11, page 15, lines 10-21). A considerable amount of experimentation was needed to make the single-step method practical (specification, Examples 2A-C, E-G, and 8). For this reason, Corey et al. neither discloses nor suggests all the limitations of Claim 1.

In addition, Corey et al. does not disclose or suggest all the limitations of Claim 5, which recites that "the sample is treated to convert living cells to dead cells prior to, simultaneously with, or after contact with the single reagent mixture, and the luminance signal generated thereby is read at any point or points in the process subsequent to addition of the reagent mixture, which may be before, after, or both before and after the conversion of live cells to dead cells." Thus, the method of Claim 5 allows independent measurements of cytotoxicity and proliferation/viability to be accomplished with a single sample. A measurement is taken before addition of a lytic agent, and a second measurement after lysis; the first measurement represents release of the test enzyme due to cytotoxicity, while the second measurement represents total biomass. Proliferation/viability is obtained by subtracting the first reading from the second. Corey et al. does not disclose or suggest independent measurements of cytotoxicity and proliferation/viability from a single sample. Indeed, such independent measurements of cytotoxicity and proliferation/viability from a single sample are not possible using the method disclosed in Corey et al. because the method disclosed in Corey et al. requires a physical separation of the live cells from the test mixture prior to performing the assay, as described above. For this reason, Corey et al. neither discloses nor suggests all the limitations of Claim 5.

For all the reasons described above, Corey et al. does not disclose or suggest all the limitations of the method of Claims 1-9. Accordingly, applicant respectfully requests withdrawal of this ground of rejection.

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Amendments to the Specification

The specification has been amended on pages 14, 22, and 37 to correct obvious grammatical errors. The amendment to the specification on page 35 corrects two inadvertent errors regarding the 5 X PGK diluent. As documented on the copy of the original page of Dr. Corey's notebook dated July 31, 2000 (enclosed as Appendix A), the amount of NaCl used was 1.5 g, not 15 g, and the components of the 5 X PGK diluent are made up to final volume of 50 mL.

New Claim 21

New Claim 21 depends from Claim 1 and recites that the high-energy molecule is at least one of NADH, NADPH, or ATP. This limitation was present in Claim 1 as originally filed, but has been deleted from Claim 1 to overcome the indefiniteness rejection as described above.

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CONCLUSION

In view of the foregoing amendments and remarks, Claims 1-21 are believed to be in condition for allowance. If any issues remain that can be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicant's attorney at 206.695.1783.

Respectfully submitted,

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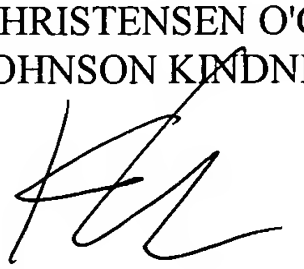

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Enclosure:
Appendix A

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: 4/13/04 Carole Julyan

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